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# Anesthetic Management of the Newborn Surgical Patient

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Additional information is available at the end of the chapter

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## Abstract

Providing anesthesia for the newborn requires many considerations beyond what is needed for the older child or adult. This chapter discusses pertinent anesthetic considerations in the care of surgical neonates including preoperative evaluation, intraoperative management and pain management techniques.

**Keywords:** neonatal anesthesia, anesthetic agents, pain management

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## 1. Introduction

Advances in pediatric anesthesiology have contributed to improved outcomes and survival in newborns requiring surgical intervention. Newborn physiology is characterized by a high metabolic rate, limited cardiopulmonary reserve, and decreased renal function. Multisystem organ immaturity underlies the differences in physiologic response to anesthetics in the neonate when compared to the older child or adult. This chapter discusses physiologic considerations, preoperative evaluation and preparation, intraoperative anesthetic management, and pain management techniques unique to the newborn surgical patient.

## 2. Physiologic considerations

### 2.1. Cardiovascular

Fetal cardiac circulation is characterized by two right-to-left shunts: one through the foramen ovale and one through the ductus arteriosus. With the infant's first breaths, the lungs expand,

alveolar fluid is cleared, pulmonary vascular resistance markedly decreases, and left atrial pressure increases [1]. These physiologic changes promote functional closure of the fetal cardiac shunts and mark the beginning of the transition from fetal to newborn circulation.

Anatomic closure of the foramen ovale typically occurs within the first year of life, though some studies indicate over one quarter of foramen ovale remain echocardiography probe patent into adulthood [2]. Functional closure of the ductus arteriosus is achieved between 10 and 15 hours of life, and anatomical closure is usually completed by 2 months of age [3]. Neonatal circulation may revert to fetal circulation if the physiological parameters responsible for cardiac shunt closure are not maintained. As such, it is important to avoid factors that increase pulmonary vascular resistance (physiologic stress, hypoxia, hypercarbia, acidosis, and hypothermia) in newborns. Hypervolemia may also promote reopening of the ductus arteriosus and should be avoided.

Maintenance of heart rate is essential in the neonatal period. Cardiac output is dependent on heart rate, as stroke volume is fixed due to decreased compliance of the immature ventricle [4]. Thus, while maintaining preload is important during anesthetic management, increasing preload provides minimal benefit for improving cardiac output. The sympathetic nervous system is also immature in newborns. Bradycardia may occur after stimulating procedures such as laryngoscopy, oropharyngeal suctioning, or gastric tube placement rather than the expected tachycardia seen in patients with mature sympathetic nervous systems. Treatment with anticholinergics may be required.

## 2.2. Pulmonary

Development of the respiratory system begins during fetal organogenesis and continues throughout childhood. Alveolarization starts at 28 weeks of gestational age, and by 40 weeks, alveoli are present at 20–50% of adult values. Type 2 pneumocytes, the main producers of surfactant, appear at approximately 24 weeks of gestational age but are not fully functional until 34–36 weeks of gestational age [5].

Neonates are an increased risk for respiratory fatigue. High chest wall compliance may cause a paradoxical breathing pattern when large breaths are taken [5]. Newborns have a reduced number of fatigue-resistant high-oxidative diaphragmatic muscle fibers; mature levels are not reached until 8 months of age [6]. Neonatal oxygen requirements are 2–3 times the adult requirement, ranging from 6 to 9 mL/kg/min. Increased oxygen demand is met by increased respiratory rate, as there is a minimal inspiratory reserve to increase tidal volume [7].

Neonatal respiratory drive is determined by  $pO_2$  via peripheral chemoreceptors in the carotid bodies and by  $pCO_2$  influencing central chemoreceptors in the medulla. Respiratory drive is primarily affected by hypoxia, as opposed to hypercarbia in adults. Administration of high oxygen concentrations may depress respiratory drive in the newborn [8].

## 2.3. Renal

The kidneys are fully developed anatomically by 34–36 weeks of gestational age but continue to develop functionally after birth. The glomerular filtration rate (GFR) is initially decreased

in the neonate due to low systemic arterial pressure and high renal vascular resistance but increases during the first several weeks of extrauterine life [9]. As a result of this initial low GFR, there is a decreased ability of the kidneys to maintain electrolyte balance or clear drugs and excess fluids.

## 2.4. Neurologic risk

The neurologic system is anatomically complete at term, though synaptogenesis and nerve myelination continue throughout childhood. Data from animal studies, as well as retrospective human studies, have raised concern that exposure to anesthetic agents could be detrimental to cognitive development in young children due to effects either on synaptogenesis or apoptosis of the developing brain [10]. The stage of brain development at the time of exposure and the degree of anesthetic exposure, in terms of both exposure frequency and cumulative anesthetic dose, may affect the risk of neurotoxicity.

The SmartTots program, a partnership between the United States Food and Drug Administration and the International Anesthesia Research Society, was established in 2009 to address the growing concern regarding potential adverse consequences of general anesthesia in young children. Two consensus statements, published in 2012 and 2015, counsel that the effect of exposure to anesthetic drugs in young children is unknown. Some, but not all, studies to date have suggested that problems similar to those seen in animals could also occur in infants and toddlers. The benefits of elective procedures must be weighed against the risks associated with anesthesia and surgery [11].

## 3. Preoperative evaluation and preparation

### 3.1. History and physical examination

A thorough preanesthetic history and physical examination must be performed with the goals of identifying potential anesthetic complications due to coexisting disease, determining whether further diagnostic studies are required prior to surgery and anticipating postoperative concerns including pain management and level of cardiorespiratory monitoring required.

Factors that should be addressed in the preanesthetic history are outlined in **Table 1**. A review of all organ systems, including identification of genetic syndromes and associated anomalies, should be completed. Examination of previous anesthetic and surgical records may reveal difficulties with airway management, venous access, or anesthetic emergence and assist in planning future anesthetic management.

Physical examination should assess for evidence of coexisting diseases (e.g., craniofacial abnormalities, congenital heart disease, chronic lung disease). Hydration status may be determined by evaluating skin turgor, mucous membranes, fontanelle fullness, and urine output. Existing intravenous catheters should be examined for patency and hypovolemia treated prior to anesthetic induction. Laboratory studies must be reviewed and significant electrolyte abnormalities and/or anemia corrected preoperatively.

The American Society of Anesthesiologists (ASA) physical status classification system is used as a uniform system for describing the degree of patient morbidity prior to an anesthetic (**Table 2**) [12]. The grading system is not intended for use as a measure to predict operative risk.

Factor	Specific concerns
Maternal history during pregnancy	Rh-ABO compatibility Diabetes Toxemia Infection Drug or alcohol abuse
Gestational age and weight	Extreme prematurity and/or extremely low birth weight
Significant birth events	Apgar scores Neonatal asphyxia Meconium aspiration
Perinatal course	Apneas Supplemental oxygen requirement Need for ventilator support
Medications and medication allergies	Type and severity of adverse medication reaction

**Table 1.** Factors to address in the preanesthetic history.

Physical score classification*	Definition
ASA I	A normal healthy patient
ASA II	A patient with mild systemic disease
ASA III	A patient with severe systemic disease
ASA IV	A patient with severe systemic disease that is a constant threat to life
ASA V	A moribund patient who is not expected to survive without the operation
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes

\*Emergency cases are designated by the addition of “E” to the classification number.

**Table 2.** American Society of Anesthesiologists physical status classification system.

3.2. Fasting

Infants are required to fast before procedures requiring sedation and anesthesia in order to minimize the risk of pulmonary aspiration of gastric contents [13]. Fasting times are based on pediatric gastric emptying studies. **Table 3** provides a summary of fasting recommendations

by the ASA [14]. Prolonged fasting may lead to hypovolemia and hypoglycemia in infants; glucose-containing intravenous maintenance fluids should be administered prior to the induction of anesthesia.

The majority of pediatric aspiration events occur during anesthetic induction [15]. Risk factors for aspiration in the perianesthetic period include neurologic abnormality, emergency surgery, intestinal obstruction or increased abdominal pressure, light anesthesia, and the skill of the anesthesia provider [16, 17]. Infants and young children are particularly prone to regurgitation and aspiration for a variety of reasons including air swallowing while crying and decreased lower esophageal sphincter incompetence. In one study, almost all cases of pulmonary aspiration occurred in children who gagged or coughed during airway management, either because neuromuscular blockade was not administered or airway manipulation occurred before the child was completely paralyzed [15]. Mortality due to pulmonary aspiration is low, with an estimated incidence between zero and 1:50,000 [15, 16, 18].

Ingested material	Minimum fasting period (hours)
Clear liquids	2
Breast milk	4
Infant formula	6
Nonhuman milk	6
Light meal	6

**Table 3.** American Society of Anesthesiologists fasting recommendations.

### 3.3. Postoperative apnea in former premature infants

Postoperative apnea is defined as cessation of breathing or no detectable airflow for 15 seconds or longer, or less than 15 seconds with bradycardia. It has been observed in former premature infants after exposure to all forms of anesthetics (intravenous agents, inhalational agents, and regional anesthesia) [19–21]. The incidence of postoperative apnea varies inversely with gestational age at birth and post-conceptual age at the time of surgery. Apnea risk is greater than 1% until 54 weeks of post-conceptual age or 56 weeks of post-conceptual age in infants with a gestational age of 32 or 35 weeks, respectively [22].

Former preterm infants who are less than 60 weeks of post-conceptual age at the time of surgery should be monitored until free of apnea for at least 12 hours. A monitored bed should be arranged for the postoperative period, and family members should be educated regarding the risk of perianesthesia apnea. Children receiving theophylline or caffeine preoperatively should have these medications continued postoperatively [23]. Caffeine administration does not negate the need for postoperative respiratory monitoring. Factors such as anemia, hypothermia, hypoglycemia, hypocalcemia, acidosis, and hypoxemia may increase the risk of apnea and should be avoided.



## 4. Intraoperative management

### 4.1. Monitoring and intravenous access

The ASA's Standards for Basic Anesthetic Monitoring mandates continual evaluation of oxygenation, ventilation, circulation, and temperature during all anesthetics [24]. Placement of both a pre-ductal oxygen saturation monitor on the right upper extremity and a post-ductal oxygen saturation monitor on a lower extremity should be considered in neonates as a means to detect right-to-left shunting across the ductus arteriosus [25]. A nerve stimulator may be used if neuromuscular blocking agents are administered, though the train-of-four response is often diminished in infants less than 2 months old. It is imperative that the operating room be kept warm. Neonates, especially premature infants, are at high risk for heat loss due to an increased surface area to volume ratio when compared to older children and adults [26, 27]. The need for invasive monitoring, including arterial and central venous catheter placement, is determined by the baseline medical condition of the patient and the extensiveness of the planned surgery. Arterial catheters allow for continuous monitoring of heart rate and blood pressure, as well as arterial blood gas sampling [28]. Central venous catheters are utilized when large intravenous access is necessary, central venous pressure monitoring is required, or in hemodynamically unstable conditions likely to require continuous vasopressor infusions. The benefits of placement must always be weighed against the risks associated with use, such as catheter-associated bloodstream infection [29]. A urinary catheter should be considered in surgical cases of prolonged duration or when significant blood loss is expected.

### 4.2. Anesthetic agents

Most infants arriving as outpatients for surgery may undergo mask induction of anesthesia with inhaled anesthetic agents. Those patients presenting from inpatient hospital wards or the neonatal intensive care unit (NICU) with intravenous access in situ may undergo intravenous induction of general anesthesia [27].

#### 4.2.1. Inhaled anesthetic agents

Inhaled halogenated anesthetics (most commonly sevoflurane, isoflurane, and desflurane) are used for both induction and maintenance of general anesthesia. The minimum alveolar concentration (MAC) is the end-tidal concentration of inhaled anesthetic agent at which 50% of patients do not move in response to a noxious stimulus. MAC values are used to compare the relative potencies of anesthetic agents and vary with age for each particular agent (**Table 4**) [30–32]. Of note, MAC values may differ for preterm neonates depending upon the inhalational agent used and the gestational age of the infant.

Sevoflurane is the halogenated agent most commonly chosen for mask induction of anesthesia; its use is associated with a reduced incidence of breath holding, coughing, laryngospasm, and oxygen desaturation when compared with other inhaled anesthetics [30]. Nitrous oxide, a nonhalogenated agent, may be used in conjunction with halogenated

Characteristic	Sevoflurane	Desflurane	Isoflurane	Nitrous oxide
MAC adult	2.05%	7.0%	1.2%	104%
MAC neonate (full term)	3.2%	9.2%	1.6%	–

**Table 4.** Minimum alveolar concentration (MAC) values for modern inhalational anesthetics.

inhaled anesthetics to speed inhalational induction (“second-gas effect”) or reduce halogenated agent doses during the maintenance phase of anesthesia. Nitrous oxide must be used with caution as it may rapidly diffuse into and expand gas-filled body cavities. Its use should be avoided in laparoscopic surgery and is contraindicated in patients with a pneumothorax [33].

#### 4.2.2. Intravenous anesthetic agents

Similar to inhaled halogenated anesthetics, intravenous anesthetic agents may be utilized for both induction and maintenance of anesthesia. Agent choice is commonly based upon the following drug properties: speed of onset, duration of action, cardiovascular stability, and side-effect profile [34].

Propofol is an intravenous agent with sedative-hypnotic properties resulting from gamma-aminobutyric acid (GABA)-mediated inhibitory neurotransmission. Systolic blood pressure falls approximately 15% after propofol administration due to decreases in preload, cardiac contractility, and systemic vascular resistance. Propofol is a potent respiratory depressant, and apnea may occur transiently after bolus administration. Pain on injection may be attenuated with intravenous lidocaine administration.

Ketamine is a phencyclidine derivative that antagonizes N-methyl-D-aspartate (NMDA) receptors. This results in a “dissociative”-type anesthesia and a potential for disturbing dreams or delirium. Ketamine possesses excellent amnestic, analgesic, and bronchodilation properties. Administration is associated with favorable hemodynamic parameters except in catecholamine-depleted patients. The use is limited in patients with a history of seizure disorder and in those in whom increases in intracranial and/or intraocular pressures would be detrimental. Nystagmus, myoclonus, and copious oral secretions are frequent side effects of ketamine use.

Etomidate depresses the reticular activating system and mimics the inhibitory effects of GABA. It possesses minimal effects on the hemodynamic system but can decrease ventilatory drive. Induction doses are known to transiently inhibit enzymes involved in cortisol and aldosterone synthesis with the potential for adrenocortical suppression.

Thiopental is a barbiturate that acts by prolonging the duration of GABA-mediated chloride channel opening. Administration can cause cardiovascular depression that is accentuated in the hypovolemic patient. Compared to other induction agents, acute tolerance to thiopental may develop, and prolonged sedation can be noted after induction doses [35].



### 4.2.3. Neuromuscular blocking agents

Neuromuscular blocking drugs allow for patient immobility, smooth endotracheal intubation, increased tolerance of mechanical ventilation, and optimal surgical relaxation. They are classified into two groups, depolarizing and non-depolarizing agents, based on activity at the neuromuscular junction [36]. The choice of drug depends on the desired speed of onset, duration of action, route of elimination, and side-effect profile.

Succinylcholine is the only depolarizing agent currently available for clinical use. An increased dose of succinylcholine is necessary in infants due to relative effect resistance at the neuromuscular junction and the larger volume of distribution in the neonate. Succinylcholine is metabolized by circulating pseudocholinesterase. It has a very rapid onset (60 seconds) and short duration of action (5 minutes). Succinylcholine carries an FDA “black box warning” against routine use in children due to risk of hyperkalemic cardiac arrest in patients with undiagnosed neuromuscular disorders [37]. Thus, it is recommended that the use of succinylcholine in children be reserved for emergency intubation or instances where immediate securing of the airway is necessary (e.g., laryngospasm, difficulty airway, full stomach) [38].

Non-depolarizing neuromuscular blocking agents are divided into intermediate (atracurium, cisatracurium, rocuronium, and vecuronium) and long-acting (pancuronium) varieties [26]. Neuromuscular blocking drugs are responsible for over 35% of anesthetic-related hypersensitivity reactions and should be considered as potential causes if anaphylaxis is suspected in the peri-anesthetic period. The effects of non-depolarizing muscle relaxants may be antagonized by an anticholinesterase (neostigmine or edrophonium) administered in conjunction with an anticholinergic agent (glycopyrrolate or atropine) to minimize parasympathetic side effects. Successful reversal of neuromuscular blockade in infants is demonstrated by adequate return of strong hip and/or arm flexion, abdominal muscle contraction, and return of the train-of-four twitch response to four equal twitches.

Historically, neuromuscular blocking drugs could only be reversed after adequate time had elapsed to demonstrate some natural return of neuromuscular function. Sugammadex, a cyclodextrin oligosaccharide, is a new reversal agent that inactivates steroidal neuromuscular blocking agents such as vecuronium and rocuronium via direct encapsulation. This mechanism allows for rapid and complete reversal of neuromuscular blockade within minutes of administration of a neuromuscular blocking agent. Studies examining sugammadex use in children aged 2–18 years suggest no evidence of higher incidence of adverse effects with sugammadex compared to that with neostigmine or placebo [39]. Data regarding the safety of sugammadex in infants are currently limited.

## 4.3. Fluid and blood product management

Calculating total intraoperative fluid requirements necessitates considering fluid type, maintenance fluid requirements, evaporative fluid losses, and replacement of intraoperative blood loss.

### 4.3.1. Glucose requirements

Healthy infants and children can remain euglycemic for up to 17 hours despite fasting. Infants receiving total parenteral nutrition or 10% dextrose in water (D10W) preoperatively require continued

glucose replacement intraoperatively [27, 40]. Glucose levels naturally increase intraoperatively secondary to decreased insulin sensitivity from release of surgery-related stress hormones.

#### 4.3.2. Maintenance fluid requirements

Maintenance fluid requirements are determined by accounting for water losses from the renal, pulmonary, and gastrointestinal systems in addition to calculating baseline body weight and calorie usage [40]. While a variety of formulas exist to determine the maintenance fluid requirements of an infant or child, the simplest is the “4-2-1” rule shown in **Table 5** [40, 41].

D5 0.25% normal saline (NS) and D5 0.45% NS are commonly chosen maintenance fluids for children, as they closely accomplish the goal of delivering 3 mEq of sodium, 2 mEq of potassium, 2 mEq of chloride, and 5 g of glucose for every 100 mL of water administered. *Nil per os* (NPO) fluid deficit is calculated by multiplying the hourly maintenance fluid requirement by the number of hours the patient has been NPO. The NPO deficit is typically replaced intraoperatively as follows: half the total volume deficit is administered in the first hour, one quarter in the second hour, and the remaining quarter in the third hour.

Intraoperative evaporative fluid losses may be replenished with isotonic crystalloid or colloid fluids according to the following formula based on the invasiveness of surgery: superficial 1–2 mL/kg/h, moderate/intrathoracic 4–7 mL/kg/h, open intra-abdominal 6–10 mL/kg/h, and neonates with necrotizing enterocolitis >50 mL/kg/h. Current data are limited but do not support specific benefits of human albumin usage over other colloids or crystalloids in neonates [42, 43]. Favored colloid usage is institutional and region specific; many centers in the United States utilize albumin, while institutions in other nations favor hydroxyethyl starches or gelatins [44].

Weight	Hourly	Day
<10 kg	4 mL/kg	100 mL/kg
10–20 kg	40 mL + 2 mL/kg for every kg >10 kg	1 L + 50 mL/kg for every kg >10 kg
>20 kg	60 mL + 1 mL/kg for every kg >20 kg	1.5 L + 20 mL/kg for every kg >20 kg

**Table 5.** Maintenance fluid requirements by weight.

#### 4.3.3. Blood products

Estimated blood volume is calculated based on the age and weight of the patient (**Table 6**) [45]. Prior to surgery, one may calculate the maximum allowable blood loss (MABL) that would necessitate blood transfusion using the following equation:

$$\text{MABL} = \text{EBV} \times \frac{(\text{Hct current} - \text{Hct min})}{(\text{Hct current})} \quad (1)$$

where *Hct current* is the current hematocrit and *Hct min* is the minimum acceptable hematocrit.

Age	Estimated blood volume (mL/kg)
Premature infant (<37 weeks of gestational age)	100
Term infant	90
Toddler	80
School-aged child	75
Adult	65–70

**Table 6.** Calculating estimated blood volume.

Recommended doses for replacement of blood products are outlined in **Table 7** [46].

Packed red blood cells (PRBCs) have a hematocrit of approximately 55–70%. Fresh frozen plasma (FFP) administration is indicated when there is laboratory evidence of coagulopathy or significant blood loss approaching one blood volume [47]. Intraoperative platelet transfusion is more likely to be necessary with preoperative platelet counts <150,000 per mm<sup>3</sup> or after the loss of two to three blood volumes [41, 48]. Massive blood loss has historically been replaced in a 1:1:1 fashion with PRBCs, FFP, and platelets. Currently, it is recommended that FFP administration begins after one blood volume has been lost or at the first sign of clinical coagulopathy [49]. It is imperative for the surgeon and the anesthesiologist to maintain excellent communication regarding expectations for blood loss and proper preparation of the patient including any necessary laboratory screening tests for blood typing, antibodies, and cross matching.

Product	Dose	Expected increase
Packed red blood cells	10–15 mL/kg	Hemoglobin 2–3 g/dL
Fresh frozen plasma	10–15 mL/kg	Factors 15–25%
Platelets	5–10 mL/kg	Platelets 50–100,000/mm <sup>3</sup>
Cryoprecipitate	1–2 units/kg	Fibrinogen 60–100 mg/dL

**Table 7.** Recommended doses for replacement of blood products.

## 5. Neonatal pain management

Pain has been defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [50]. Accurately defining and quantifying pain in the neonate has challenged the medical community for decades. Neonatal pain pathways are immature and poorly understood; over 40 different pain scales have been developed to assess pain in the term and preterm neonate. Because neonates and infants cannot verbally communicate pain, regrettably their pain may go unrecognized and undertreated.

Historically, it was believed that neonates did not have the same pain perception as older infants and adults. Opioids were known to cause respiratory depression and were considered harmful; thus, postoperative analgesia with opioids was discouraged. This remained the predominant view until as late as in 1987, when research by Anand and colleagues challenged this long-standing tradition by demonstrating that unattenuated noxious or painful stimuli during neonatal cardiac surgery caused a deleterious stress response and increased morbidity. Anand published two landmark papers presenting scientific evidence that neonates experience pain and the medical necessity for treating such pain. Change in practice soon followed, accompanied by a rapid expansion of literature in this area [51–53].

Neonates in the intensive care unit are estimated to undergo as many as 14 invasive procedures associated with pain each day, with analgesia inconsistently provided for many of these procedures (**Table 8**) [54]. This is concerning as research has correlated undertreated pain in the neonatal period with long-term detrimental effects, including behavioral disorders and altered sensitivity to pain later in life [55–59].

### 5.1. Pain assessment

An ongoing challenge involves appropriately assessing and effectively treating pain in the neonate. The immature dorsal horn circuits predominantly exhibit excitatory tone, with weaker inhibitory GABA and glycine signaling. It is uncertain whether or not this lack of inhibitory processing increases the neonate's perception of pain. Flexion reflexes may be elicited with either tactile or nociceptive touch; conversely, neonates with no behavioral reaction to heel lance showed a strongly activated cortex on EEG in one study, demonstrating the inadequacy of behavioral indicators to reliably detect pain [60].

Distinguishing between pain and agitation is also difficult as there are overlapping behavioral and physiologic manifestations [61]. Facial expression (total facial activity with specific features including brow lowering, eye squeeze, nasolabial furrow, and open mouth) is considered the most sensitive behavioral indicator of acute pain. Other behavior pain indicators include body posture, limb movements, cry, consolability, and sleep/wakefulness. Physiological parameters include heart rate, respiratory rate and pattern, oxygen saturation,

Diagnostic procedures	Arterial puncture, bronchoscopy, endoscopy, heel lancing, lumbar puncture, retinopathy of prematurity examination, suprapubic bladder tap, venipuncture
Therapeutic procedures	Bladder catheterization, central line insertion/removal, chest tube insertion/removal, chest physiotherapy, dressing change, gavage tube insertion, intramuscular injection, peripheral venous catheterization, tracheal tube insertion/removal, mechanical ventilation, tracheal suctioning, postural drainage, adhesive tape removal, ventricular tap
Surgical procedures	Circumcision Other surgical procedures

**Table 8.** Commonly performed painful procedures in the neonatal intensive care unit.

and blood pressure. These parameters are also important, but less specific, as alterations may be the result of the underlying disease process rather than pain. In the mechanically ventilated neonate with neuromuscular blocking therapy, pain must be evaluated based on changes in heart rate or blood pressure. Biological markers for pain such as emotional sweating (palm or sole, measured by skin conductance or galvanic skin response) or increased stress hormones (serum or saliva cortisol) are used in research but have limited clinical utility. Among the validated neonatal pain scales, premature infant pain profile (PIPP) assesses procedural pain, and neonatal pain, agitation, and sedation scale (N-PASS) assesses ongoing pain and sedation in both term and preterm neonates, providing an advantage over other available neonatal pain assessment tools (**Table 9**) [62–65].

5.2. Therapeutic approach

Neonatal pain is best managed using a tiered approach. Painful procedures should be avoided when possible through the use of noninvasive monitoring and bundling of laboratory blood draws. Non-pharmacological therapy, such as nonnutritive sucking, oral sucrose, breast or bottle feeding, and swaddling, can be used during mildly painful events (i.e., lab draws, line insertion, removal of adhesives, wound treatment, bladder catheterization). Topical anesthetics may be used prior to skin-breaking procedures, though caution must be exercised in the preterm neonate as the epidermis is structurally and functionally immature, increasing the risk of toxicity. Acetaminophen is effective for mild pain and as an adjuvant for moderate to severe pain. Ketamine is a potent analgesic and NMDA antagonist that can be utilized during moderate to severe painful procedures of short duration or as an adjuvant to prevent opioid tolerance. Systemic opioid analgesics are utilized to treat moderate to severe pain in conjunction with the above therapies (**Table 10**) [66, 67]. Analgesic medications are most reliable when given intravenously, as oral absorption is unpredictable in the neonate [64, 68].

Pain scale	Variables included	Type of pain assessed
Premature infant pain profile (PIPP)	Heart rate, oxygen saturation, facial actions	Procedural, postoperative
Neonatal infant pain score (NIPS)	Facial expression, crying, breathing patterns, arm/leg movement, arousal	Procedural
Neonatal facial coding system (NFCS)	Facial actions	Procedural
Neonatal pain, agitation, and sedation scale (N-PASS)	Crying, irritability, facial expression, extremity tone, vital signs	Procedural, postoperative, mechanically ventilated patients
Cry, requires oxygen, increased vital signs, expression, sleeplessness (CRIES)	Crying, facial expression, sleeplessness, requires oxygen to stay at >95% saturation, increased vital signs	Postoperative
COMFORT scale	Movement, calmness, facial tension, alertness, respiration rate, muscle tone, heart rate, blood pressure	Postoperative, critical care
Douleur Aigue du Nouveau-ne (DAN)	Facial expression, limb movements, vocal expression	Procedural

**Table 9.** Summary of validated neonatal pain scales.



Medication	Intermittent dose	Infusion dose	Adverse effects
Acetaminophen	10 mg/kg IV/PO	N/A	None reported*
NSAIDS	Not recommended	N/A	Unwanted ductal closure, gastropathy, nephropathy, NEC, IVH, surgical bleeding
Morphine	0.05–0.1 mg/kg IV	0.005–0.03 mg per hour	Respiratory depression, decreased gastrointestinal motility, hypotension, urinary retention
Fentanyl	1 mcg/kg IV	0.5–2 mcg/kg per hour	Respiratory depression, hypotension, muscle rigidity, hypothermia
Ketamine	0.5–2 mg/kg IV	0.5–1 mg/kg per hour	Respiratory depression, increased secretions

NSAIDS, nonsteroidal anti-inflammatory drugs; NEC: necrotizing enterocolitis; IVH: intraventricular hemorrhage  
\*No reported adverse effects at therapeutic doses. Known hepatotoxicity with overdosing.

**Table 10.** Recommended analgesic dosing for neonates.

Postsurgical pain should be anticipated and preemptively treated to mitigate the pain and stress response. In conjunction with analgesic medications, local anesthetics may be administered as a field block, as a targeted nerve block, or as an epidural block (**Table 11**) to effectively treat procedural and surgical pain. Care must be taken during the placement of

Block	Indications
Caudal epidural block	Lower abdominal surgery, inguinal herniorrhaphy, circumcision, orchidopexy, lower limb and pelvic orthopedic surgery
Caudal epidural catheter *	<i>Lumbar level:</i> lower abdominal, pelvic, and lower limb surgery <i>Thoracic level:</i> upper abdominal, renal, or thoracic surgery
Paravertebral block (via catheter)	Unilateral thoracic or renal surgery
Intercostal nerve blocks	Thoracic surgery, multiple levels typically required
Brachial plexus block (axillary or infraclavicular)	PICC line placement, ischemic limb salvage (arterial vasodilation)
Rectus sheath block	Umbilical/paraumbilical hernia, laparoscopic surgery, pyloromyotomy
Transversus abdominis plane (TAP) block	Lower abdominal surgery
Penile block	Circumcision
Femoral nerve block	PICC line placement lower limbs, muscle biopsy, skin graft, clubfoot repair

\*Non-tunneled caudal epidural catheters should be removed after 72 hours or sooner when visible signs of soiling are present to minimize infectious risks.

**Table 11.** Neuraxial and peripheral nerve block indications.



local anesthetics, as unintended intravascular delivery can lead to systemic toxicity manifesting as altered consciousness, seizures, hemodynamic instability, and ultimately cardiovascular collapse. Safe practice includes aspiration prior to injection, slow incremental dosing, adherence to maximum dosing guidelines, and appropriate dose reductions for the neonate (**Table 12**) [69]. Local anesthetic toxicity must be promptly recognized and treated (**Table 13**) [70].

Local anesthetic	Standard maximum dose *	Recommended neonatal dose	Comments
Bupivacaine	2.5 mg/kg	1 mg/kg	Commonly used for field blocks and wound infiltration
Ropivacaine	3 mg/kg	1.5 mg/kg	Decreased motor block and cardiotoxicity compared with bupivacaine Vasoconstrictor effects (avoid using for digital and penile blocks)
Lidocaine	5 mg/kg	2.5 mg/kg	
Prilocaine	Not recommended	Not recommended	Concern for methemoglobinemia
Chloroprocaine	14 mg/kg	7 mg/kg	No plasma accumulation due to short half life
Topical anesthetic	Maximum dose		Comments
Eutectic mixture of local anesthetics (EMLA)	1 g/5 kg	1 g	Equal parts lidocaine and prilocaine Maximum skin contact 1 hour Risk of methemoglobinemia increased in premature neonates

\*Maximum doses are additive and not independent of each other; *local anesthetic dosing should be decreased by 50% in neonates.*

**Table 12.** Commonly used local anesthetics.

**Local anesthetic toxicity (LAST) management**

- Obtain help
- Managing the airway, administering 100% oxygen
- Treat seizure activity (benzodiazepines preferred)
- Alert nearest facility capable of cardiopulmonary bypass
- Support cardiovascular function (prolonged CPR, reduced epinephrine doses)
- Institute 20% lipid emulsion therapy (lipidrescue.org)

**Table 13.** Treatment of local anesthetic toxicity.

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